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EXAMINER: ZISKA, S

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DATE MAILED: 11/19/91

PRETTY, SCHROEDER, BRUEGGEMANN & CLARK
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LOS ANGELES, CA 90071

This is a communication from the examiner in charge of your application
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 9/3/91 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-18 are pending in the application.
   Of the above, claims 3, 4, 8, 9, 11, 12, 16-18 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 2, 5-7 10 13-15 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

This application should be reviewed for errors.

Applicant's election with traverse of Group I, claims 1, 2, 5-7, 10 and 13-15 in Paper No. 13 is acknowledged. The traversal is on the ground(s) that to search all the claims would not present an undue burden on the Examiner. This is not found persuasive because the inventions are distinct and have acquired a separate status in the art as shown by their different classification, recognized divergent subject matter and separate search requirements. The requirement is still deemed proper and is therefore made FINAL.

It is noted for the record that Applicants' statement of the remaining pending claims in Paper 13 was not consistent with the restriction requirement as originally stated in Paper No. 11. Thus, claims 1,2, 5-7, 10 and 13-15 are pending, not claims 1-10 and 13-15 as previously stated in the response to the restriction requirement and claims 1,2,5-7, 10 and 13-15 will be examined. Claims 3, 4, 8, 9,11, 12 and 16-18 are withdrawn from further consideration by the Examiner, 37 CFR 1,142(b) as being drawn to a non-elected invention.

Claims 1, 2, 5-7, 10 and 13-15 are rejected under 35 U.S.C. 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claim 1, the word "agent" is vague and unclear since the nature of the "agent" is indeterminate. Further regarding claim 1, Applicants have disclosed treating excised nephritic tissue with antibodies and failed to disclose treating nephritic tissue with other agents. It is not apparent that any and all other "agents" would inhibit TGF-B activity in a manner or extent similar to the antibody used. Therefore, the claim must be limited to the antibody used by Applicant. In addition, the phrase "extracellular matrix" is

vague and unclear and included many more proteins than decorin and biglycan, the two protein components actually investigated by Applicants. Therefore, the claim must be limited to the two components of the extracellular matrix actually investigated by Applicants. The phrase "suppresses the extracellular matrix producing activity" is vague and unclear since the mechanism by which this is accomplished is indeterminate and many are known in the art. Thus claims 1 and 6 in which this language occurs must be amended to specifically state the mechanism. Regarding the word "tissue", a tissue is defined (Webster's dictionary, Ninth Edition, page 1237) as an aggregate of cells usually of a particular kind together with their intercellular substance that form one of the structural materials of a plant or an animal". Applicants have used the antibodies to cells grown in a petri dish and since such pathologies as glomerulonephritis, adult respiratory distress syndrome and cirrhosis of the liver are organismal ailments, and do not occur to cells in petri dishes, the claim language of claims 1 and 6 must be amended to reflect in vitro usage only.

Regarding claims 2 and 7, the claims must be limited to the antibody actually used by Applicant for the reasons as stated above. It is not apparent that all antibodies to TGF-beta would be effective in inhibiting production of extracellular matrix since it is known in the art that antibodies do not always bind to the same epitope. In addition, it is apparent from the specification that Applicants have produced their own antibody and that this antibody is not commercially available. Thus, it is not apparent that all antibodies to TGF-beta would be as effective as those used by Applicant and so the claim must be limited to that actually used by Applicant since it is not apparent how the antibody produced by Applicant compares to those commercially available.

Regarding claim 5, the claim must be limited to glomerulonephritis since Applicants have failed to show that the treatment using anti-TGF-beta antibodies would be effective in treatment of those diseases. It is not

apparent that cirrhosis of the liver and adult respiratory distress syndrome (RDS) would be amenable to treatment with antibodies to TGF-beta since the etiology of many diseases is not known and although Applicants state that both cirrhosis and RDS are characterized by an accumulation of extracellular matrix, it is not apparent that the cause of the production is solely dependent upon TGF-beta production.

Regarding claims 6 and 13, Applicants have disclosed that antibodies to TGF-beta will inhibit synthesis of extracellular matrix but have failed to show that the antibodies will inhibit accumulation of the matrix. Note that "accumulation" of a product, in this case, extracellular matrix, is dependent upon the rate of synthesis as well as the rate of degradation and Applicants have disclosed inhibition of synthesis and not addressed the rate of degradation. Therefore, the claim language should be amended to more clearly, and accurately, describe the process as it occurrs. In addition, the phrase "extracellular matrix" is vague and unclear and included many more proteins than decorin and biglycan, the two protein components actually investigated by Applicants. Therefore, the claim must be limited to the two components of the extracellular matrix or the two proteoglycans actually investigated by Applicants.

Regarding claims 10 and 13, the claim must be limited to the kidney tissue or kidney cells, since it is not apparent that lung, liver and skin cells accumulate extracellular matrix by the same defective mechanism as do kidney cells and therefore, it is not apparent that the same treatment would be effective in other tissues.

Regarding Figure 1, Applicants report data in 8 lanes but only describe the composition of 7 lanes. It is not apparent which results correlate with which lane and therefore, the data fail to support Applicants' assertions as to the production of the extracellular matrix proteins PG I and PG II.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e., failing to provide an enabling disclosure. Applicants disclose use of an antibody to TGF-beta and further disclose that the antibody was raised against the same peptide previously shown by others to elicit antibodies. However, Applicants have failed to disclose a comparison of their antibody with those known in the art and those available to the artisan of ordinary skill. Since there is no known comparison between Applicants antibody the claims must be limited to the antibody used by Applicant.

Claims 1, 2, 5-7, 10 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

"A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States."

Claims 1, 6, 10 and 13-15 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Bassols et al. Bassols discloses that TGF-beta regulates the expression and structure of extracellular matrix chondroitin/dermatan sulfate proteoglycans. It is known in the art that decorin and biglycan are extracellular matrix chondroitin/dermatan sulfate proteoglycans. Bassols further discloses use of an agent which suppresses the extracellular matrix

producing activity of TGF-beta. See Figure 7, wherein Actinomycin D blocks expression of various TGF-beta induced proteoglycan species. Regarding claim 14, note that "mesangial" cells are a type of kidney cells, that Bassols discloses use of NKR-49F cells which are a type of kidney cell and that the NRK cell population contains mesangial cells, lacking evidence to the contrary.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1, 2, 5-7, 10 and 13-15 are rejected under 35 U.S.C. 103 as being unpatentable over Flanders et al (Biochemistry) taken with Harper et al. Flanders discloses inhibition of TGF-beta induced collagen production in NRK cells using anti-TGF-beta antisera. Flanders differs from the claims in

that the reference fails to disclose use of mesangial cells. However, the secondary reference Harper, cures the deficiencies. Harper discloses culture of mesangial cells, a type of kidney cell, obtained from the glomerulus.

It would have been obvious to one of ordinary skill to substitute the mesangial cells of Harper for the NRK cells and have a reasonable expectation of success in inhibiting the production of a proteoglycan since both cells are a type of kidney cell.

Regarding claim 5, it would have been obvious to one of ordinary skill to apply the knowledge that antiTGF-beta antibodies inhibit extracellular matrix production to those diseases characterized by extracellular matrix production in order to obtain a therapy for such diseases.

Regarding claim 15, note that decorin and biglycan are known to be among the proteoglycans comprising the "extracellular matrix" and once the ability of antibodies to TGF-beta were shown to successfully inhibit the production of extracellular matrix, it would have been obvious to one of ordinary skill to look at the production of all proteins known to comprise the "matrix" in order to determine if the method would inhibit production of all matrix proteins or a selective few. Thus, it would have been obvious to examine the synthesis of decorin and biglycan as well as collagen.

Accordingly, the modification of the method of Flanders by substituting the mesangial cell of Harper in order to obtain a method of decreasing the production of a proteoglycan in a mesangial cell was within the ordinary skill in the art at the time the claimed invention was made. From the teachings of the references, it is apparent that one of ordinary skill would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is prima facie obvious, as evidenced by the references, especially in the absence of evidence to the contrary.

No claim is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)308-4227.

An inquiry concerning this communication should be directed to Examiner Suzanne Ziska, Ph.D., at telephone number 703-308-3964.

SEZ
11/8/91

HOWARD E. SCHAIN
PATENT EXAMINER
GROUP 180-ART UNIT 186